REMARKS

Interview

Counsel wishes to thank Examiners Krass, Kunz, and Woodward for their time with regards to the Interview of October 26, 1999. The interview was clearly beneficial in resolving the issues associated with the instant application and the continuation application, Serial No. 08/460,854.

New Claims

In the amendments to independent method claim 25, the composition is described as containing the (-) enantiomer compound "or a pharmaceutically acceptable salt thereof." Similar language is recited in the independent composition claim 43. Amendments to claims 27-29, 33, 34, 37-39, 43 and 45-47 also relate to this language. New dependent claim 59 and 60 recite the (-) enantiomer compound itself. New dependent method claims 61-72 are similar to claims 27-39, except that they depend directly or indirectly on new claims 59 or 60. New dependent composition claims 73-77 are similar to claims 45-54, except that they depend directly or indirectly on claim 49. New claims 78-80 relate to combined administration. See, e.g., page 9, lines 4-6 of applicants' specification. New claims 81-88 are similar to claims 25, 26, 43, 44, 48 and 59 but do not require a carrier.

Formal Issues

In the Office Action of August 12, 1999, the Examiner pointed out two typographical errors in claim 25. These errors, as well as a typographical error in claim 50, are eliminated by the above amendments. Claims 33 and 34 are amended so that there is express antecedent basis for terms recited therein.

Rejection Under 35 U.S.C. § 112, second paragraph

In the Office Action, the Examiner questions whether the dependency of claim 48 on claim 43 is proper. Claim 43 recites the (-) enantiomer compound "or a pharmaceutically acceptable salt thereof." Conversely, claim 48 recites the (-) enantiomer compound itself. Therefore, it is respectfully submitted that claim 48 is definite and properly dependent on claim 43. Withdrawal of the rejection under 35 U.S.C. §112 is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 25-29, 31-34, 37-39 and 43-48 are rejected under 35 U.S.C. §103 in view of Liotta et al. (US 5,539,116) and Belleau et al. (US 5,047,407). This rejection is respectfully traversed.

Presently, there is an Interference (No. 104,201) between Belleau et al. application Serial No. 08/468,362 and Liotta et al.'s US '116. The Belleau et al. application claims priority back to Belleau et al .US '407. The count of the Interference is directed to single enantiomers of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one.

Prior to the declaration of Interference No. 104,201, there was pending litigation in Georgia between Emory University (assignee of US '116) and BioChem Pharma (assignee of US '407) and Glaxo-Wellcome (BioChem Pharma's licensee) (*Emory University v. GlaxoWellcome Inc.*, D.C. Ga. No. 1:96-CV-1868-GET). This litigation was stayed as a result of the Interference being declared.

As noted above, the interference count concerns a single enantiomer whereas the claims of this application are directed to the (-)-enantiomer specifically and another agent having antiviral activity. However, if there are any documents from the litigation or interference which the Examiner wishes to review, applicants will provide copies thereof. The following is a list of the substantive Preliminary Motions filed by each of the Parties in the above-mentioned Interference:

Belleau's Preliminary Motions against Liotta's '116:[1]

1) Motion for Judgment based on Anticipation;
2) Motion for Judgment based on Obviousness
3) Motion for Denial of Benefit Based on Lack of Written Description;
4) Motion for Judgment Based on Lack of Written Description;
5) Motion for Judgment Based on New Matter;
6) Motion for Judgment Based on Inequitable Conduct;
12) Motion for Denial of Benefit on Lack of Enablement (Contingent).

Liotta's Preliminary Motions against Belleau's Application:

1) Motion for Judgment Based on Inequitable Conduct;
2) Motion for Judgment Based on Lack of Enablement;

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[1]Belleau's Preliminary Motions 7-11 related to adding of claims, adding proposed counts, and benefit with respect to proposed counts.

3) Motion for Judgment Based on Lack of Best Mode;

4) Motion for Denial of Benefit;

5) Motion for Denial of Benefit;

6) Motion for Judgment Based on Anticipation (Contingent)

As can be gathered from the above list of Preliminary Motions, Belleau's position is that Liotta et al.'s '116 is invalid. Belleau also takes the position in the Interference that its original 308,101 application (which issued as US '407) supports claims directed to single enantiomers of the racemate known as BCH-189 [*cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane]. Of course, Liotta (Emory) takes the opposite views.

US '116 states: "the other enantiomer is inactive and, therefore, represents a 50% impurity." See column 3, lines 44-47. US '116 does not identify which enantiomer is inactive and which is not. Thus, US '116 does not identify the (-) enantiomer as being the active one. In fact, the U.S. '116 disclosure does not disclose data on antiviral activity or cytotoxicity for any compound, whether in racemic or enantiomeric form.

The US '116 disclosure is in fact wrong. Both the (-) and the (+) enantiomers are active. See applicants' specification at page 2, lines 3-7.

If one assumes solely for the sake of argument that Liotta does disclose the (-)-enantiomer compound (a point Belleau contests in the interference), Liotta's disclosure would still not render obvious applicants' claimed method and composition. The US '116 disclosure does not disclose or suggest selecting the (-)-enantiomer of BCH-189, and then further combining this compound with another agent having antiviral activity. As acknowledged in the Office Action, US '116 does not disclose the combining of any of the compounds described therein with another agent having antiviral activity.

Furthermore, the '116 disclosure in no way suggests the unexpectedly advantageous results associated with use of the (-)-enantiomer. As discussed in applicants specification, the (-) enantiomer compound of the claimed invention possesses an exceptional activity profile. First of all, it possesses significant antiviral activity (see Tables 1 and 2 at page 28 of applicants' specification). This fact itself is surprising because the (-)-enantiomer possesses the unnatural "L-like" configuration. As discussed in the articles cited below, in the past, biologically active nucleoside analogues almost always had the natural D-like configuration.

In addition, the (-)-enantiomer exhibits significantly low cytotoxicity, e.g., compared to the (+)-enantiomers. See applicants' specification at page 2, lines 4-7 and Table 3 at page 29. Toxicity of the (-)-enantiomer is even lower than that of AZT, the only approved drug for

the treatment of HIV infection at the time of applicants' priority date. See also the discussion of the articles below.

Thus, the (-)-enantiomer is an exceptional antiviral agent unexpectedly possessing both high activity and low toxicity making it particularly suitable for combing with other antiviral agents in the treatment of HIV infections. These unexpected results associated with applicants' claimed combination of the (-) enantiomer and another agent having antiviral activity is in no way suggested by the disclosure of the US '116 alone or in combination with anything else.

Belleau et al. US '407 discloses the (-)-enantiomer compound and the (+)-enantiomer compound. See, e.g., Formula (XI) at column 7, Example 7 (b) at column 12, and the disclosure at column 5, lines 34-37. US '407 also discloses using compounds of formulas I, II and III, "with any other drug." See column 8, lines 57-65. However, as with the disclosure of US '116, the disclosure of US' 407 does not suggest that by selecting the (-)-enantiomer compound recited in applicants' claims and combining this compound with another antiviral agent one would achieve the unexpected results discussed above. This is because the latter properties were first discovered by the inventors.

To further explain the unexpected properties of the (-)-enantiomer, enclosed herewith are copies of the following three articles, all of which were published in 1992:

Beach et al., "Synthesis of Enantiomerically Pure (2'R,5'S)-(-)-1-[Hydroxymethyl)oxathiolan-5-yl]cytosine as a Potent Antiviral Agent against Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV)," *J. Org. Chem.* 1992, 57, 2217-2219;

Chang et al., "Deoxycytidine Deaminase-resistant Stereoisomer Is the Active Form of (±)-2',3'-Dideoxy-3'-thiacytidine in the Inhibition of Hepatitis B Virus Replication," *Journal of Biological Chemistry*, July 15, 1992, Vol. 267, No. 20; and

Schinazi et al., "Activities of the Four Optical Isomers of 2',3'-Dideoxy-3'-Thiacytidine (BCH-189) against Human Immunodeficiency Virus Type 1 in Human Lymphocytes," *Antimicrobial Agents & Chemotherapy*, March 1992, Volume 36, No. 3.

Beach et al. discusses the antiviral properties of the two enantiomers of BCH-189. Referring to Table I at page 2218, compound 1 is the racemate BCH-189, compound 2 is the (+)-enantiomer (also referred to in this case as the "D" enantiomer or the enantiomer with the natural-like configuration), and compound 3 is the (-)-enantiomer recited in applicants' claims, (also known as the "L" enantiomer or the enantiomer with the unnatural-like

configuration). As can be seen from the test results presented in Table I, the (-)-enantiomer exhibits significantly lower toxicity than the (+)-enantiomer or the racemate (see also the comment at page 2219, right column, lines 5-6).

Beach et al. characterizes the activity profile of the (-) enantiomer as unexpected. In the Summary at page 2217, it is stated that: "This is the first example of an 'L-like' nucleoside which is more potent than its 'D-like' isomer." See also the last paragraph at page 2219 which refers to the high anti-HIV activity of the (-) enantiomer. They also acknowledge that "the β-D-isomers of nucleosides are in general the biologically active isomers."

The Schinazi et al. article (reference no. 8 in the Beach article) discloses both the high HIV activity and low cytotoxicity of the (-) enantiomer. See Table 2 at page 674. This compound is shown to have comparable anti-HIV activity to AZT (see also page 673, right column, lines 12-19), yet significantly lower cytotoxicity (in CEM cells and Vero cells). Schinazi also acknowledges the prior expectation that the "D" nucleoside would be the biologically active isomer: "All natural nucleosides and most biologically active nucleoside analogs have the β-D configuration."

Chang et al. uses the acronym (-)-SddC to refer to the (-)-enantiomer. As with the articles discussed above, Chang et al. notes that the activity of the (-)-enantiomer is unexpected: "This is the first nucleoside analog with the unnatural sugar configuration demonstrated to have antiviral activity." See the summary in the top left column of page 13938.

In view of the above remarks, it is respectfully submitted that neither Liotta US '116 not Belleau US '407, taken alone or in combination, renders obvious applicants' claimed invention. Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

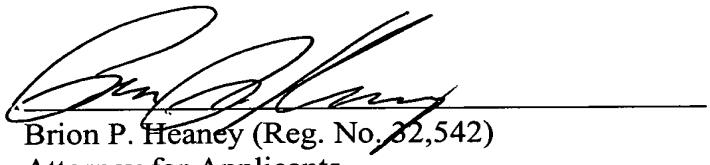
Obviousness-Type Double Patenting Rejection

In the Office Action it is asserted that claims 25-29, 31-34, 337-39, and 43-58 are provisionally rejected for obviousness-type double patenting in view of claims 30,31 and 33-74 of continuation application Serial No. 08/460,854. However, for purposes of obtaining an early allowance of the instant application, applicants will submit a terminal disclaimer with respect to the continuation application. Submission of the terminal disclaimer is not to be construed as an acquiescence in any ground of rejection.

In view of the above remarks, favorable consideration and allowance of the above claims is respectfully requested.

As a final note, as was discussed at the October 28, 1999, interview, Cheng et al. (U.S. 5,756,478 and U.S. 5,869,461, both having effective filing dates of March 16, 1995) claims a composition and method in which a toxicity reducing amount of specified L-nucleosides is combined specifically with D-nucleosides. This concept is narrower than the generic concept reflected in applicants' claims. Importantly, the PCT publication essentially identical to this application (WO 91/17159) was published (November 14, 1991) more than 3 years prior to Cheng's filing. Thus, the disclosure of this application is indisputably §102 prior art against Cheng. Applicants will seek an interference with U.S. '478 via the continuation application 08/460,854.

Respectfully submitted,



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